DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

**TRANSMITTED BY FACSIMILE**

Mr. Dan Oren, President and Chief Executive Officer
Dexcel Pharma Technologies Ltd.
1 Dexcel Street
Or Akiva 30600
Israel

**RE: NDA #20-774**
**PerioChip® (chlorhexidine gluconate) 2.5 mg**
**MACMIS #17470**

# WARNING LETTER

Dear Mr. Oren:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional journal advertisement (ADV MIS_4) for PerioChip® (chlorhexidine gluconate) 2.5 mg (PerioChip) submitted by Lachman Consultant Services, Inc. on behalf of DEXCEL® PHARMA TECHNOLOGIES LTD (Dexcel) under cover of Form FDA 2253. The journal advertisement is false or misleading because it presents safety and efficacy claims for PerioChip but the body of the advertisement fails to communicate **any** information about the risks associated with the product. The journal advertisement also overstates the efficacy of PerioChip, makes misleading claims, and omits material facts about the drug. Thus, your journal advertisement misbrands PerioChip in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(n) & 321(n), and FDA implementing regulations. 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i), (vii), (xvii), (xviii) & (e)(7)(iii).

## Background

According to the **INDICATIONS AND USAGE** section of the approved product labeling (PI):

> PerioChip is indicated as an adjunct to scaling and root planning procedures for reduction of pocket depth in patients with adult periodontitis. PerioChip may be used as part of a periodontal maintenance program, which includes good oral hygiene and scaling and root planing.

Additional information regarding the appropriate use of PerioChip is presented in the **DOSAGE AND ADMINISTRATATION,** which states:

> One PerioChip is inserted into a periodontal pocket with probing pocket depth (PD) ≥ 5 mm. Up to 8 PerioChips may be inserted in a single visit. Treatment is recommended to be administered once every three months in pockets with PD remaining ≥ 5 mm.

The periodontal pocket should be isolated and the surrounding area dried prior to chip insertion. The PerioChip should be grasped using forceps (such that the rounded end points away from the forceps) and inserted into the periodontal pocket to its maximum depth. If necessary, the PerioChip can be further maneuvered into position using the tips of the forceps or a flat instrument. The PerioChip does not need to be removed since it biodegrades completely.

The **CONTRAINDICATIONS**, **PRECAUTIONS**, and **ADVERSE REACTIONS** sections of the PI state (in pertinent part):

**CONTRAINDICATIONS**
PerioChip should not be used in any patient who has a known sensitivity to chlorhexidine.

**PRECAUTIONS**
**General**
The use of PerioChip in an acutely abscessed periodontal pocket has not been studied and therefore is not recommended. Although rare, infectious events including abscesses and cellulitis, which have been reported after scaling and root planing alone, have also been reported with the adjunctive placement of the PerioChip post scaling and root planing. Management of patients with periodontal disease should include consideration of potentially contributing medical disorders, such as cancer, diabetes, and immunocompromised status.

**Information for Patients**
Patients should avoid dental floss at the site of PerioChip insertion for 10 days after placement, because flossing might dislodge the chip. All other oral hygiene may be continued as usual. No restrictions regarding dietary habits are needed. Dislodging of the PerioChip is uncommon; however, patients should be instructed to notify the dentist promptly if the PerioChip dislodges. Patients should also be advised that, although some mild to moderate sensitivity is normal during the first week after placement of PerioChip, they should notify the dentist promptly if pain, swelling, or other problems occur.

**. . .**

**ADVERSE REACTIONS**
The most frequently observed adverse events in the two pivotal clinical trials were toothache, upper respiratory tract infection, and headache.

**Omission of Risk Information**

Promotional materials are misleading if they fail to reveal material facts in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. Your journal ad makes numerous safety and efficacy claims for PerioChip, including claims that PerioChip is "**Safe** for repeated use" (emphasis in original) and "Patients can eat, drink and brush normally following PerioChip placement." However, the body of the journal ad entirely omits risk

information for PerioChip, including the contraindication, precautions, and most frequently reported adverse events from the PI. We note that the Brief Summary is included on the second page of the ad, but this is not sufficient to provide appropriate qualification or pertinent information for the claims made in the body of the ad. Promotional materials must contain risk information in each part as necessary to qualify any safety or effectiveness claims made (21 CFR 202.1(e)(3)(i)).

**Overstatement of Efficacy/Misleading Claims**

Promotional materials are misleading if they state or suggest that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience. The journal ad includes the following claim:

> "The use of PerioChip® + SRP resulted in a clinically meaningful improvement compared to SRP alone … **5x** the number of pockets were reduced from 7-8 mm to 2-4 mm[1]" (emphasis in original).

This claim misleadingly overstates the effectiveness of PerioChip by suggesting that PerioChip will reduce pocket depth by 3-6 mm in five times the number pockets compared to scaling and root planning (SRP) alone. You reference the Soskolne article to support this claim. This reference does not constitute substantial evidence to support this claim. Although the above statement is consistent with Figure 4 in the reference (30% vs. 6% is a 5x improvement), the information displayed in this figure is derived from a post-hoc subgroup analysis. As a general matter, when looking for differences between treatment groups, a study must be designed to look for these differences prospectively. The Soskolne study was not designed in this way, and thus does not constitute substantial evidence to support this efficacy claim. We are not aware of other data constituting substantial evidence or substantial clinical experience to support this claim.

Moreover, the five fold efficacy claim is inconsistent with the efficacy results demonstrated in the pivotal clinical trials for PerioChip and reflected in its PI. According to Table 2 in the Clinical Studies section of the PI, approximately twice as many subjects treated with Periochip + SRP as subjects treated with SRP alone showed an improvement in pocket depth of 2 mm or more at 9 months (22% (PerioChip + SRP) vs. 11% (SRP alone) in Study 002 and 16% (PerioChip + SRP) vs. 6% (SRP alone) in Study 003).

The journal ad also includes the following claim:

> "PerioChip …
> o Suppresses pocket flora **up to 11 weeks[2] post treatment**" (emphasis in original).

The journal ad references the Stabholz article to support this claim; however, this article does not constitute substantial evidence or substance clinical experience. The Stabholz article

[1] Soskolne W.A. et al. Sustained local delivery of Chlorhexidine in the treatment of Periodontitis: a multi-center study. J Perio; 1997;68:32-8.
[2] Stabholz et al. Clinical and microbiological effects of sustained release chlorhexidine in periodontal pockets. J Clin Perio; 1986;13:783-788.

explains that “sustained release devices” with chlorhexidine were placed at baseline and **every 3 days for the first 9 days** of the trial. The dosing regimen for the study described in this article is completely inconsistent with the approved dosing regimen reflected in PerioChip’s PI, which recommends that PerioChip be administered at baseline and then once every three months in pockets with PD remaining ≥ 5 mm. Furthermore, the article does not refer to the product used in the study as “PerioChip” and does not describe the product’s composition in any detail. Rather, the product is called a “sustained release device.” It is therefore not clear that the product tested in the Stabholz article is identical to the currently marketed PerioChip, particularly as the article was published in 1986 and PerioChip was not approved until 1998.

(b) (4)

Lastly, the journal ad includes the following claim:

> “**PerioChip** allows for **PRECISION PLACEMENT** which can be accomplished in **less than 1 minute**” (emphasis in original).

Three pictures are tiled horizontally underneath the claim, and what appears to be a one-minute clock icon appears above each picture. The first (leftmost) picture shows tooth scaling and the minute clock above this picture is at approximately 20 seconds, and the second and third pictures show placement of PerioChip and the minute clocks above these pictures are at 30 seconds and approximately 50 seconds, respectively. This presentation misleadingly suggests that both tooth scaling and the placement of PerioChip can be accomplished within one minute. While it is possible for a dentist to accomplish placement of PerioChip within one minute, it is not possible for the dentist to accomplish both the scaling and placement of a PerioChip within one minute, as suggested by this presentation.

**Omission of Material Fact**

The journal ad omits the material fact that PerioChip is recommended for use in periodontal pockets with a pocket depth (PD) greater than or equal to 5 mm. Specifically, the Dosage and Administration section of the PI states, “One PerioChip is inserted into a periodontal pocket with probing pocket depth (PD) ≥5 mm. Up to 8 PerioChips may be inserted in a single visit. Treatment is recommended to be administered once every three months in pockets with PD remaining ≥ 5 mm.” As a result of this omission, the journal ad misleadingly suggests that this product has been demonstrated to be effective for use in periodontal pockets of any depth.

Additionally, the journal ad includes the claim, “Slow release of Chlorhexidine **for 7-10 days**” (emphasis in original). However, as reflected in the Pharmacokinetics section of the PI, PerioChip releases chlorhexidine *in vitro* in two distinct phases, “initially releasing

approximately 40% of the chlorhexidine within the first 24 hours and then releasing the remaining chlorhexidine in an almost linear fashion for 7-10 days." By omitting this material information regarding the initial release characteristics of chlorhexidine, this claim misleadingly suggests that the product releases chlorhexidine at a constant slow rate over 7-10 days, when this is not the case. Moreover, this claim is also misleading because it fails to reveal that the release profile is based on an *in vitro* analysis, and thus suggests that this information is derived from clinical observations when this is not the case.

**Conclusion and Requested Action**

For the reasons discussed above, your professional journal advertisement misbrands PerioChip in violation of the Act, 21 U.S.C. 352(n) and 321(n), and FDA's implementing regulations. 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i), (vii), (xvii), (xviii) & (e)(7)(iii).

DDMAC requests that Dexcel immediately cease the dissemination of violative promotional materials for PerioChip such as those described above. Please submit a written response to this letter on or before May 29, 2009, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) in use for PerioChip as of the date of this letter, identifying which of these materials contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, or facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS #17470 in addition to the NDA number. We remind you that only written communications are considered official. If you choose to revise your promotional materials, DDMAC is willing to assist you with your revised materials by commenting on your revisions before you use them in promotion.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for PerioChip comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications

CC: Mary-Anne D'Esposito, M.Sc., Manager (US Agent)
Lachman Consultant Services, Inc.
1600 Stewart Avenue
Westbury, New York 11590

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/s/

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Thomas Abrams

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